PROSTATE SPECIFIC ANTIGEN FOR ASSESSING RESPONSE TO KETOCONAZOLE AND PREDNISONE IN PATIENTS WITH HORMONE REFRACTORY METASTATIC PROSTATE CANCER

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ABSTRACT

Serial prostate specific antigen levels were assessed in 15 patients with hormone refractory metastatic prostate cancer treated with ketoconazole and prednisone. Of the men 12 (80%) with continually increasing prostate specific antigen levels before treatment had a decrease in prostate specific antigen with a median duration of response of 3 months. Three patients (20%) had a prolonged response (greater than or equal to 8 months) as seen by a persistently decreasing prostate specific antigen and improvement in bone pain. There appears to be a small subgroup of patients with progressive prostate cancer despite androgen ablation who will benefit from ketoconazole and glucocorticoid treatment. The use of serial prostate specific antigen levels appears to help define this subgroup and avoid the need for multiple radiological procedures to assess response. (*J. Urol., 144: 1177–1179, 1990*)

Ketoconazole was originally developed as an antifungal agent effective against a wide variety of pathogenic fungi.[1] However, it also was noted that this drug is a potent inhibitor of gonadal and adrenocortical steroid synthesis.[2, 3] In addition, an in vitro cytotoxic effect on prostate cancer cells was demonstrated.[4] These findings suggested a potential role for ketoconazole in the treatment of prostate cancer. Initially, the drug was used with favorable results in patients with previously untreated stage D2 disease.[5–7] However, in men with hormone refractory metastatic prostate cancer, results with ketoconazole have not been as promising.[6–9] Jubelirer and Hogan reported findings in 16 of their patients and they reviewed the literature concerning ketoconazole use in men with disease progression despite adequate hormonal therapy.[8] They noted that complete and partial responses to ketoconazole were seen in less than 1 and 14% of the patients, respectively. The criteria to assess response in these studies were varied but generally included reduction in measurable tumor size, improvement in bone scan abnormalities and/or decrease in acid phosphatase level. None of the reports used serial prostate specific antigen (PSA) levels to assess clinical response. While changes in PSA are a good indicator of disease activity in men with metastatic prostate cancer treated with hormonal manipulation,[10] the role of PSA changes in patients treated with second line hormonal agents in unclear. Therefore, we were prompted to investigate the changes in PSA in men with hormone refractory metastatic prostate cancer treated with a combination of ketoconazole and prednisone.

MATERIALS AND METHODS

A total of 15 patients with hormone refractory metastatic prostate cancer was treated with ketoconazole and prednisone. Of the patients 14 had undergone orchiectomy a minimum of 5 months before treatment, while 1 had been treated with injections of a luteinizing hormone-releasing hormone agonist for 17 months before therapy. The latter patient had an anorchid serum testosterone level when treatment with ketoconazole and prednisone was begun and he was maintained on the luteinizing hormone-releasing hormone agonist while on ketoconazole and prednisone. All patients had histologically proved adenocarcinoma of the prostate and bone scan evidence of metastatic disease at the onset of hormonal therapy. The median duration of response to hormonal therapy, as assessed by stable or decreasing PSA levels and no progression of bone pain, was 14 months (range 2 to 50 months).

Unresponsiveness to the initial hormonal therapy was defined as an increasing PSA level on 2 consecutive determinations that were at least 1 month apart. All 15 patients satisfied this requirement. In addition to increasing continually PSA levels 12 patients had bone pain and/or other symptoms of widespread malignancy at the onset of ketoconazole and prednisone therapy. The remaining 3 patients were asymptomatic. Failure on ketoconazole and prednisone therapy was defined as an increasing PSA level on 2 consecutive determinations.

Of 15 patients 10 had previously received radiotherapy. No patient received radiation concurrently with ketoconazole and prednisone. Of these 10 patients 9 had evidence of progressive disease (increasing PSA levels) after the completion of radiotherapy and before initiation of ketoconazole and prednisone, while 1 had a lower PSA level after radiation and was treated with ketoconazole and prednisone because of continued bone pain. The median interval from completion of radiotherapy to the onset of treatment with ketoconazole and prednisone in the 10 patients was 8 months (range 2 weeks to 5 years).

Serum PSA levels were determined with the Hybritech Tandem-R assay in most cases. In several patients the Yang Pros-Check assay was used before a change in the methodology used by the laboratory at our hospitals. While each assay has a different range of normal values, both have been shown to be reliable with highly reproducible results.[11, 12] Some studies have suggested that variables, such as bed rest and hospitalization, may cause a substantial decrease in PSA levels.[11, 13] In addition, prostate manipulation, especially core biopsy, may cause increases in serum PSA levels.[13] To control for these factors all PSA levels were determined in ambulatory patients seen in the outpatient clinic. Prostate manipulation or cystoscopy always was performed after a serum sample for PSA determination had been collected.

Although some patients were initially analyzed with the Yang assay and then subsequently analyzed with the Hybritech method, none of the positive responses was the result of changing the assay method (figs. 1 to 3).

Patients were initially treated with 600 to 900 mg. ketocon-

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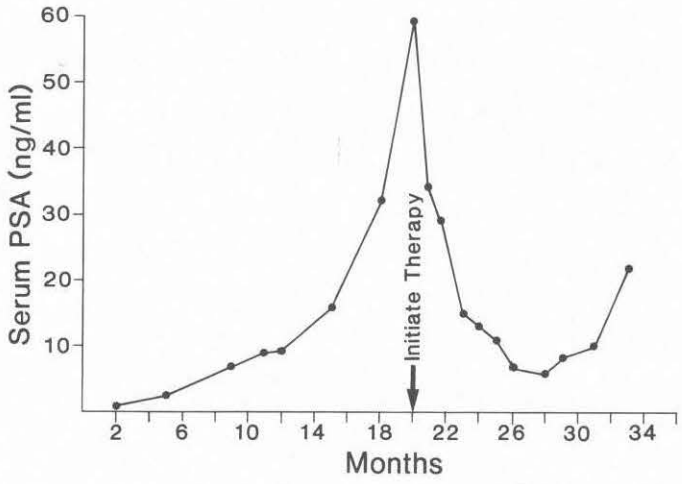

FIG. 1. Changes in PSA for patient 1 who was initially treated by bilateral orchiectomy and then ketoconazole and prednisone were initiated when PSA was 60 ng./ml.

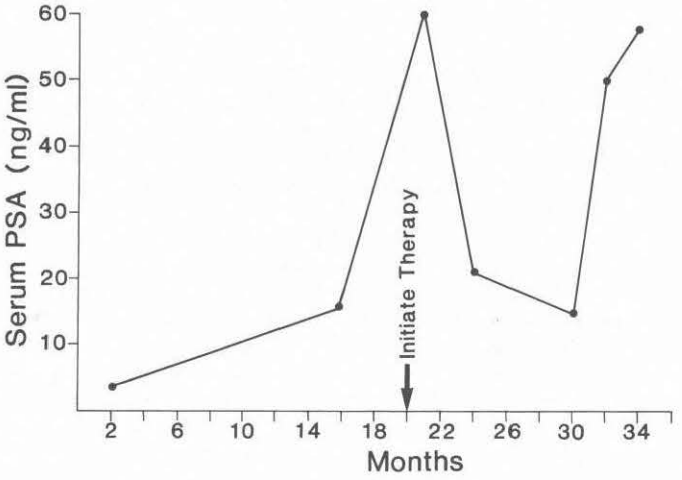

FIG. 2. Patient 2 had increasing PSA despite bilateral orchiectomy and focal radiation. Ketoconazole and prednisone were initiated when PSA was 60 ng./ml.

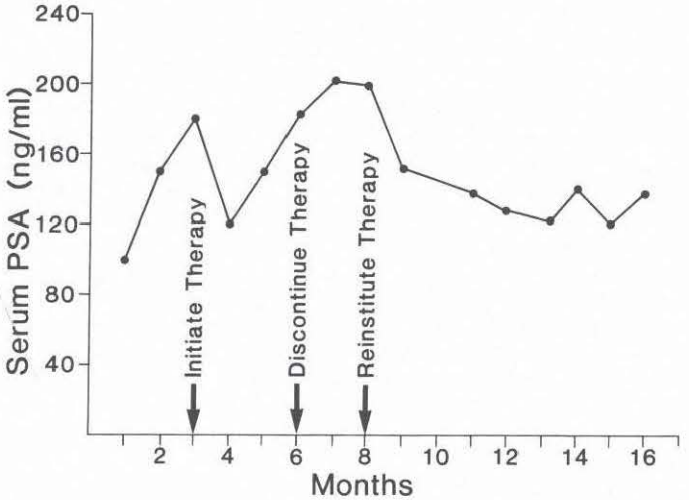

FIG. 3. Patient 3 initiated ketoconazole and prednisone after PSA increased from 100 to 180 ng./ml. After short response PSA again increased and medication was discontinued. Patient began therapy again because of increasing pain and PSA stabilized.

azole daily in 3 divided doses and 5 mg. prednisone twice per day. PSA levels were recommended monthly and the ketoconazole dosage was increased to 1,200 mg. daily in 3 divided doses if the PSA did not decrease. At the time of each visit patients also underwent history and physical examination, and they were specifically questioned regarding treatment-related side effects. Liver function tests were evaluated along with each serum PSA level.

RESULTS

Of the 15 patients 12 (80%) with hormone refractory prostate cancer showed a decrease in PSA in response to ketoconazole and prednisone with a median duration of response of 3 months. The mean decrease in PSA in the 12 responding patients was 49% of the pre-treatment level (mean 312 ng./ml., range 38 to 1,717, before treatment and 138 ng./ml., range 6 to 347, after treatment). Twelve patients also had bone pain and/or other symptoms of advancing malignancy, of whom 9 (75%) had subjective improvement. The decrease in PSA corresponded to subjective improvement in symptomatic patients with 1 exception. One patient had a 7% decrease in PSA during 4 months of treatment but he had no improvement in bone pain. One patient who had no decrease in PSA did have a decrease in bone pain. The mean peak PSA level before treatment in the nonresponding patients was 300 ng./ml.

The duration of response to ketoconazole and prednisone was 4 months or less in 9 of the 12 responding men (75%). However, 3 patients had a prolonged response of 8 to 10 months (see table). Patient 1 underwent radical prostatectomy in 1984 at which time he had stage D1 disease. Bone metastases subsequently developed and he was treated with bilateral orchiectomy in 1986. In December 1988 a steadily increasing PSA level as well as bone pain were noted and the patient was treated with ketoconazole and prednisone (fig. 1). The bone pain resolved and the PSA level decreased rapidly until September 1989 when it began to increase again. Patient 2 was diagnosed with stage D2 disease in 1983 and underwent bilateral orchiectomy. Back pain developed due to bony metastases and he was treated with local radiotherapy through May. Before radiation the PSA level was 16 ng./ml. and 3 months after treatment it increased to 60 ng./ml. (fig. 2). In addition, the back pain recurred and a bone scan showed progressive disease. He was treated with ketoconazole and prednisone beginning in August 1988. Subsequently, the back pain improved and the PSA level decreased. In January 1989 the bone scan showed stable disease and he remained clinically well until June, when the bone pain worsened and the PSA increased rapidly. He died shortly thereafter. Patient 3 underwent radiotherapy for localized prostate cancer in 1984. In 1987 bone metastases developed and he was treated with bilateral orchiectomy. He remained stable until November 1988, when the PSA level had increased to 180 ng./ml. and the bone scan showed progressive disease. The patient was asymptomatic at this time. He was treated with ketoconazole and prednisone, and after an initial decrease in PSA the level began to increase again 2 months later, at which time the drugs were discontinued (fig. 3). Subsequently, bone pain developed and the patient self-administered ketoconazole and prednisone. At the next outpatient clinic visit he reported complete resolution of the bone pain

PSA levels in long-term (more than 6 months) responders to ketoconazole and prednisone

Pt. No.	Pre-Treatment Peak PSA Level Ng./Ml.	Post-Treatment Nadir PSA Level Ng./Ml. (% decrease)	Mos. of Response	Subjective Improvement
1	58	6 (90)	10	Yes
2	60	15 (75)	10	Yes
3*	180	122 (32)	2	Asymptomatic
	206	123 (40)	8	Yes

* Received second course of therapy after initial progression.

and the PSA level had decreased from 198 to 155 ng./ml. He remained asymptomatic with a steadily decreasing PSA until November 1989 when the pain recurred and the PSA increased slightly. Nevertheless, he was maintained on ketoconazole and prednisone and the PSA has continued to fluctuate near its nadir level.

Ketoconazole was generally well tolerated. One patient had nausea and vomiting requiring discontinuation of the drugs after 1 month of treatment. Two patients suffered minor bruising believed to be secondary to prednisone. No significant elevation in liver function studies was observed.

DISCUSSION

After the demonstration of diminished adrenocortical and gonadal steroid synthesis by ketoconazole,[2] several investigators reported results with this drug in men with untreated metastatic prostate cancer.[5-7] The combined results of these trials showed a response rate in excess of 80%. However, in patients with disease progression despite adequate hormonal therapy the objective response rate with ketoconazole has been less than 15%.[8] Based on the latter results Jubelirer and Hogan concluded that ketoconazole as a single agent has limited use in patients who have failed prior hormonal therapy for advanced prostate cancer.[8] In contrast to this conclusion Trump and associates stated that there may be a small subset of patients with hormone refractory disease who will benefit from ketoconazole treatment.[14] They found that 5 of 36 patients had a greater than 50% decrease in tumor mass or a regression of disease on bone scan when treated with the combination of ketoconazole and physiological glucocorticoid replacement therapy. Since it is apparent that a small but reasonable percentage of men failing standard hormonal therapy will respond favorably to ketoconazole, it is important to identify these patients as objectively as possible. Recent studies with PSA suggested that this marker could be useful to identify the patients who respond to ketoconazole.

While it generally is accepted that PSA changes correlate with disease activity[10] the significance of these changes in men treated with second-line hormonal agents is unclear. Of the 5 responding patients in the series reported by Trump and associates 4 had a greater than 80% decrease in PSA.[14] However, several patients with clinical evidence of disease progression had either stable or diminished PSA levels. These investigators concluded that over-all PSA changes did not reliably reflect disease response or progression.

In our study 12 of 15 castrated patients (80%) with progressively increasing PSA levels had a decrease in PSA in response to treatment with ketoconazole and prednisone. While this improvement in PSA was short-lived (less than or equal to 4 months) and occasionally of small magnitude in 9 of the 12 men, it did correlate with subjective improvement in symptomatic patients in all but 1 instance. The importance of short-term decreases in PSA is unclear, although it is unlikely that significant impact on survival will be seen in these cases. These transient PSA decreases may partially explain the disease progression in patients with stable or diminished PSA levels seen by Trump and associates.[14] Of our 3 patients in whom the PSA level continued to increase despite treatment with ketoconazole and prednisone, 1 reported a transient decrease in bone pain. In general, therefore, changes in PSA correlated well with symptomatology.

Of our patients 3 (20%) have had prolonged (8 to 10 months) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement. This rate of response is similar to that found in studies that have used changes in measurable tumor size, bone scan abnormalities and acid phosphatase to assess response.[8, 14] Thus, it appears that serial PSA levels may be useful to define the small subgroup of men failing standard hormonal therapy who will benefit from the combination of ketoconazole and prednisone. The use of PSA may then obviate the need for repeated bone scans, chest radiographs, and abdominal and pelvic computerized tomography scans to assess disease response. In our experience approximately 10% of the patients will have a low PSA despite progressive metastatic disease and their response will have to be assessed by other methods.

In summary, as in the report by Trump and associates[14] there appears to be a small subgroup of patients with progressive prostate cancer despite hormonal therapy who will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy. The presence of a persistent (greater than or equal to 6 months) decrease in PSA, as well as prolonged relief of symptoms may help to define these patients and avoid the need for multiple radiological procedures to assess response. Short-term decreases in PSA are of unclear importance but probably do not reflect significant disease regression.

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